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(57) Abstract

A method of treating or preventing, in a person, one or more symptoms of migraine headaches, said method comprising oral administration or by a transdermal delivery system or patch to said person a composition comprising one or more purified isoflavonoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitein, equol and dihydrodaidzein and their conjugates.

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ISOFLAVONOIDS FOR TREATMENT AND PREVENTION OF MIGRAINE HEADACHES

BACKGROUND OF THE INVENTION

The present invention relates to therapies for the prevention and treatment of migraine headaches and menstrual-related headaches and the symptoms associated with these headaches, particularly in women.

It is recognized that a rapid decrease in estrogen levels during the menstrual cycle can cause migraine headaches. Men, in lesser numbers, also suffer from migraine, for unknown physiologic reasons. Migraine headaches are characterized by some (but not necessarily all) of the following symptoms: unilateral onset of headache; moderate to severe throbbing or pulsating head pain; photophobia (light sensitivity); premonitory aura of visual changes (blurry vision and/or flashing lights); speech difficulties; and hemiparesis (weakness or paralysis on one side). Approximately 20% of individuals experiencing a migraine headache report symptoms for a duration of four to six hours and 80% report a duration of six hours to more than twenty-four hours. In the United States between 17 and 19% of women have experienced symptoms of migraine headaches or menstrual-related headaches.

In women, about 60% of migraine headaches occur at plus or minus a two-day interval from onset of menstruation. The high frequency of migraine at menstruation is believed to result from the rapid decrease of estrogens in the blood at this time in the menstrual cycle. A subcutaneous implant of a capsule containing estradiol, which results in a slow release of the estrogen, has been used to delay and prevent migraine headaches.

In areas of the world where soy products are consumed in great quantities as part of the regular diet, migraine headaches are less common than

in Western countries. Thus, the incidence of migraine headaches among Japanese women is 40% lower than the incidence among American women. In addition, the incidence of migraine headaches among elderly Chinese women is approximately 50% lower than that among age-matched American women.

Blood levels and urinary excretion of isoflavonoids have been studied in different population groups eating a regular diet containing either high or low amounts of isoflavonoids. In one study, Japanese women who consumed soy products on a regular basis excreted 12 to 64 times more daidzein and 41 to 59 times more equol than American or Finnish women. In addition, Japanese women excreted 106 times more genistein than Finnish women. These findings indicate that populations consuming a natural diet rich in soy products have high blood and serum levels of isoflavonoids. In another line of research, administering a soy dietary supplement with large amounts of isoflavonoids to Western subjects (from Australia and Canada) produced high levels of isoflavonoids in the blood and urine. In one such study performed with Australian women, it was found that oral supplementation with 45 grams of soy powder, which would be equivalent to 70 mgs of total isoflavonoids, increased the blood level of equol from 0.48 ng/ml to 31.1 ng/ml after two weeks. Similarly, the blood daidzein concentration increased from 5.0 ng/ml to 68.1 ng/ml. In a similar study conducted jointly in Canada and Finland it was found that men drinking a soy beverage experienced a 110-fold increase in the level of genistein and a 150-fold increase in daidzein in their blood. These data indicate that ingestion of a dietary product containing isoflavonoids results in a significant increase in the level of these compounds in the bloodstream.

Migraine headaches are currently treated with a host of synthetic drugs that alter neurotransmitter levels or influence cerebral blood flow and can have serious side effects. Safer and effective therapies for migraine headaches

continue to be sought.

SUMMARY OF THE INVENTION

The invention features the use of purified isoflavonoids, which are constituents of soy beans and other plants such as clover, to effectively treat and prevent symptoms of headaches, in particular migraine headaches, that are caused by reduced or altered levels of endogenous estrogen. Migraine-like headaches in men are also treated with purified isoflavonoids according to the invention. Without being bound by any theory, it is believed that the isoflavonoids bind to estrogen receptors and activate cellular signal induction, and thus exert an estrogenic response. These compounds are safe and cause no significant side-effects. Purified isoflavonoids which may be administered according to the invention include genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitein, equol and dihydrodaidzein and their conjugates; these may be administered alone or in combination.

Accordingly, the invention provides a method for treating or preventing symptoms of migraine headache by administering (preferably orally) to the person a composition containing one or more purified isoflavonoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitein, equol, and dihydrodaidzein and their conjugates in an amount sufficient to produce a transient isoflavonoid concentration in the bloodstream of the person of at least 10 ng/ml. Preferably, the composition is administered orally, providing a dosage of at least 20 mg of total isoflavonoid per serving. The orally-administrable composition can be a non-naturally occurring dietary product such as a confectionary bar, cereal, biscuit, or beverage. Alternatively, the composition can take the form of a medicament such as a pill, capsule, tablet, powder, or syrup, in which the total isoflavonoid is present in at least an amount of 20 mg per unit dose.

Preferably, the dietary product or medicament is orally consumed by the person once, twice, or three times per day, to provide a daily oral isoflavonoid dose of between 20 and 300 mg. Preferably, the oral ingestion of the composition is sufficient to produce in the bloodstream of the person a transient concentration of total isoflavonoid of at least 10 ng/ml. By "purified" isoflavonoid is meant an isoflavonoid in more concentrated form than occurs in plants. Preferably, each isoflavonoid administered according to the invention is at least 3%, more preferably at least 30% pure by weight.

Alternatively, the isoflavonoid-containing composition can be included in a transdermal delivery system or patch.

Other features and advantages of the invention will be apparent from the Detailed Description thereof, and from the claims.

DETAILED DESCRIPTION

Isoflavonoids are naturally occurring compounds, found primarily in soy beans. These compounds are also found in high concentrations in red clover and in lower amounts in many other types of plants. An isoflavonoid-containing fraction (containing purified isoflavonoids) useful in the invention can be extracted from a soy or plant product using known methods. It is preferred that the isoflavonoids be extracted and concentrated from soy beans or soy powder, but other plants such as clover can be used. An isoflavonoid-containing fraction can be extracted from a soy or plant product in concentrations between 3 and 30% isoflavonoids. Isoflavonoids are also available commercially in substantially pure form.

The concentrated isoflavonoid is preferably administered either in pill, capsule, tablet, powder, or syrup form, or as an additive to a flavored drink, or as a component of a confectionary bar, biscuit, or cereal containing suitable flavoring to constitute a palatable product.

An isoflavonoid-containing transdermal patch can be of conventional form, e.g., that used to deliver sustained doses of nicotine or estrogen. Isoflavonoids have similar chemical properties to estrogens, e.g., they are poorly soluble in water but are readily soluble in alcohols and other organic solvents. For use in a patch, the isoflavonoid is mixed in a base with ingredients such as alcohol, mineral oil, glyceryl monostearate, an ether complex of fatty acids, acetyl alcohol, lanolin, propylene glycol, stearyl alcohol, and sodium lauryl sulfate. The concentration of isoflavonoid is 1 to 40 mg per gram of the base, more preferably 10 to 25 mg per gram of base.

Other embodiments are within the claims.

We claim:

1. Use of one or more purified isoflavonoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitein, equol and dihydrodaidzein and their conjugates, alone or in combination, in the preparation of a medicament to treat or prevent migraine headache by producing, upon administration, a transient isoflavonoid concentration in the bloodstream of a person of at least 10 ng/ml.

2. The use of claim 1, wherein said composition is formulated for oral administration, in a dosage of at least 20 mg of isoflavonoid per serving.

3. The use of claim 2, wherein said composition is in the form of a non-naturally occurring dietary product.

4. The use of claim 3, wherein said dietary product is a confectionary bar.

5. The use of claim 3, wherein said dietary product is a cereal.

6. The use of claim 3, wherein said dietary product is a biscuit.

7. The use of claim 3, wherein said dietary product is a beverage.

8. The use of claim 1, wherein said composition is in the form of a medicament.

9. The use of claim 8, wherein said composition contains at least 20 mg/unit dosc of isoflavonoid.

10. The use of claim 8, wherein said medicament is in the form of a pill,

capsule, tablet, powder, or syrup.

11. The use of claim 1, wherein said composition is carried on a transdermal delivery system or patch.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11532

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A61K 31/55, 31/12
US CL : 514/456, 685
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/456, 685

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,204,369 A (VALLEE et al) 20 April 1993, col. 12-13.	1-11
Y,P	US 5,807,586 A (JACKSON et al) 15 September 1998, see entire document.	1-11
Y,P	Database EUROPATFUL on STN, AN 765668 BREATON et al. 'Extract of Iridaceas and compositions containing it'. EP 765668 B1 17 March 1999, see abstract and entire document.	1-11

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